OT 2 4 2003 N

PTO/SB/08a/b (06-03)
Approved for use through 07/31/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
perwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Substitute for form 1449A/B/PTO

1

Sheet

## INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

of

4

| Complete if Known      |                   |  |
|------------------------|-------------------|--|
| Application Number     | 10/615,716        |  |
| Filing Date            | July 8, 2003      |  |
| First Named Inventor   | Mladen MERCEP     |  |
| Art Unit               | TBA               |  |
| Examiner Name          | TBA               |  |
| Attorney Docket Number | 03818/100L650-US1 |  |

|                         | U.S. PATENT DOCUMENTS |                             |   |                     |                              |  |
|-------------------------|-----------------------|-----------------------------|---|---------------------|------------------------------|--|
| Examiner                | 144.5514.64           | Document Number             | Publication Date                                | Name of Patentee or | Pages, Columns, Lines, Where |  |
| Initials*               |                       | Applicant of Cited Document | Relevant Passages or Relevant<br>Figures Appear |                     |                              |  |
| Luga                    | 1.                    | 6,297,260                   | 10/02/2001                                      | Bandarage et al.    |                              |  |
| (g*                     | 2.                    | 4,710,495                   | 12/01/1987                                      | Bodor               |                              |  |
| شون                     | 3.                    | 6,402,733                   | 06/11/2002                                      | Daugherty           |                              |  |
| <i>Ĺ</i> <sub>2</sub> . | 4.                    | 6,273,086                   | 08/14/2001                                      | Ohki et al.         |                              |  |
| (1                      | 5.                    | 6,228,346                   | 05/08/2001                                      | Zhang et al.        |                              |  |
| У                       | 6.                    | 5,747,467                   | 05/05/1988                                      | Agouridas et al.    |                              |  |
| ′ُزيا                   | 7.                    | 4,474,768                   | 10/02/1984                                      | Bright              |                              |  |

|                       |              | FOREI  | GN PATENT                   | DOCUMENTS  |   |          |
|-----------------------|--------------|--|-----------------------------|--|---|----------|
| Examiner<br>Initials* | Cite<br>No.1 | Foreign Patent Document  Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>3</sup> (If known) | Publication Date MM-DD-YYYY | Name of Patentee or<br>Applicant of Cited Document | Pages, Columns, Lines,<br>Where Relevant Passages<br>or Relevant Figures Appear | T⁰       |
| 6,1                   | 8.           | WO 94/13690  | 06/23/1992                  | Rhone-Poulenc Rorer Limited                        |   | H        |
| 67"                   | 9            | WO 94/14834  | 07/07/1994                  | Rhone-Poulenc Rorer Limited                        |   | -        |
| ٠,,                   | 10.          | WO 92/13873  | 08/20/1992                  | Aktiebolaget Astra                                 | -   |          |
| رة                    | 11.          | WO 92/13872  | 08/20/1992                  | Aktiebolaget Astra                                 |   |          |
| ť                     | 12.          | WO 00/42055  | 07/20/2000                  | Zambon Group S.P.A.                                |   |          |
|                       | 13.          | EP 0283055   | 08/29/1990                  | Sour Pliva farmaceutska                            |   |          |
|                       | 14.          | EP 0775489   | 05/28/1997                  | Taisho Pharmaceutical Co.<br>Ltd.                  |   |          |
| · ,                   | 15.          | EP 0771564   | 05/07/1997                  | Taisho Pharmaceutical Co.<br>Ltd.                  |   |          |
| ٠,٧.                  | 16.          | WO 97/41255  | 11/06/1997                  | Massachusetts Institute of Technology              |   |          |
| · ii                  | 17.          | EP 00680967  | 10/14/1998                  | Hoechst Marion Roussel                             |   |          |
| 19                    | 18.          | WO 99/51616  | 10/14/1999                  | Pliva, Farmaceutska                                |   |          |
| 6-23                  | 19.          | EP 0984019   | 03/08/2000                  | Pfizer Products Inc.                               |   |          |
| <u>., </u>            | 20.          | WO 98/56801  | 12/17/1998                  | Pfizer Products Inc.                               |   |          |
| 41,                   | 21.          | WO 94/14834  | 07/07/1994                  | Rhone-Poulenc Rorer Limited                        |   |          |
| 1                     | 22.          | EP 0984019 A1  | 03/08/2000                  | Pfizer Products Inc.                               |   | $\dashv$ |
| ζ,                    | 23.          | WO 98/56801  | 12/17/1998                  | Pfizer Products Inc.                               |   |          |

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. I Applicant's unique citation designation number (optional). See Kinds Codes of USPTO Patent Documents at <a href="https://www.uspto.gov">www.uspto.gov</a> or MPEP 901.04. Senter Office that issued the document, by the two-letter code (WIPO Standard ST.3). For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. Applicant is to place a check mark here if English language Translation is attached.

| Examiner  | ( 0 . 6  | Date 27 . 7       |
|-----------|----------|-------------------|
| Signature | 4, riali | Considered (1970) |
|           |          |                   |

PTO/SB/08a/b (06-03)
Approved for use through 07/31/2003. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE uperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Complete if Known Application Number 10/615,716 **INFORMATION DISCLOSURE** Filing Date July 8, 2003 STATEMENT BY APPLICANT Mladen MERCEP First Named Inventor Art Unit **TBA** (Use as many sheets as necessary) TBA Examiner Name 03818/100L650-US1 2 4 Attorney Docket Number Sheet of

|                      |                          | NON PATENT LITERATURE DOCUMENTS   |    |
|----------------------|--------------------------|---|----|
| Examiner<br>Initials | Cite<br>No. <sup>1</sup> | Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.         | T² |
| Co                   | 24.                      | Gladue R. P. et al.,"In Vitro and In Vivo Uptake of Azithromycin (CP-62,993) by Phagocytic Cells: Possible Mechanism of Delivery and Release at Sites of Infection," <i>Antimicrob. Agents and Chemother.</i> , 33. 1989, 277-282                                       |    |
| 4-                   | 25.                      | Olsen K. M. et al., "Intrapulmonary Pharmacokinetics of Zithromycin in Healthy Volunteers Given Five Oral Doses," Antimicrob. Agents and Chemother.,40, 1996, 2582-2585   |    |
| 4                    | 26.                      | Mikasa, K. et al., "The anti-Inflammatory effect of erythromycin in zymosan-Induced peritonitis of mice," J. Antimicrob. Chemother., 30, 1992, 339-348  |    |
| Cyr                  | 27.                      | "Discussion, Genomic organization of axolotl 1g genes," J. Immunol., 159, 1997, 3395-4005   |    |
| 'n                   | 28.                      | Takizawa, H. et al., "Erythromycin Modulates IL-8 Expression in Normal and Inflamed Human Bronchial Epithelial Cells," Am. J. Respir. Crit. Care Med., 156, 1997, 266-271   |    |
| γ,                   | 29.                      | Labro, M.T., "Anti-inflammatory activity of macrolides: a new therapeutic potential?" <i>J. Antimicrob. Chemother.</i> 41, 1998, 37-46  |    |
| ė,                   | 30.                      | Cazzola, M., et al., "Potential role of macrolides in the treatment of asthma," Mondaldi Arch. Chest Dis., 55, 2000, 231-236  |    |
|                      | 31.                      | Avila, P.C. et al., "Macrolides, asthma, inflammation, and infection," Ann. Allergy Asthma Immunol, 84, 2000, 565-568   |    |
| <b>'</b> y           | 32.                      | Amayasu, H. et al., "Clarithromycin suppresses bronchial hyperresponsisveness associated with eosinophilic inflammation in patients with asthma," <i>Ann. Allergy, Asthma &amp; Immunol</i> , 84, 2000, 594-598   |    |
| ٠,٠                  | 33.                      | Shoji, T. et al., "Anti-inflammatory effect of roxithromycin in patients with aspirin-intolerant asthma," Clin. Exp. Allergy, 29, 999, 950-956  |    |
| ζ,                   | 34.                      | Griffith, E.C., et al., "Yeast Three-Hybrid System for Detecting Ligand-Receptor Interactions,"<br>Methods in Enzymology, 328m 2000, 89-110   |    |
| ζ,                   | 35.                      | Denis A. et al., "Synthesis and Antibacterial Activity of HMR 36K47, A New Ketolide Highly Potent Against Erythromycin-Resistant and Susceptible Pathogens," <i>Bioorg. &amp; Med. Chem. Lett</i> , 9, 1999, 3075-3080  |    |
| ري.                  | 36.                      | Agouridas C. et al., "Synthesis and Antibacterial Activity of Ketolides (6-O-Methyl-3-oxoerythromycin Derivatives): A New Class of Antibacterials Highly Potent against Macrolide-Resistant and -Susceptible Respiratory Pathogens," J. Med. Chem., 41, 1998, 4080-4100 |    |
| (j)                  | 37.                      | Sun, Or Y. et al. J. Med. Chem. 2000, 43, 1045-1049   |    |
|                      | 38.                      | McFarland, J. W. et al., "Repromicin Derivatives with Potent Antibacterial Activity against<br>Pasteurella multocida," J. Med. Chem., 50, 1997, 1041-1045   |    |
| i,                   | 39.                      | Denis A. et al., "Synthesis of 6-O-Methyl-Azithromycin and Its Ketolide Analogue via Beckmann Rearrangement of 9(E)-6-O-Methyl-Erythromycin Oxime, <i>Bioorg.&amp; Med. Chem. Lett.</i> , 8, 1998, 2427-2432  |    |
| ۲,                   | 40.                      | Lartey et al., "Synthesis of 4"-Deoxy Motilides: Identification of a Potent and Orally Active Prokinetic Drug Candidate, <i>J. Med. Chem.</i> , 38, 1998, 1793-1798   |    |

| Examiner  | 1 2 1      | Date              |
|-----------|------------|-------------------|
| Signature | 7. Millian | Considered 3/5/29 |



PTO/SB/08a/b (06-03)

Approved for use through 07/31/2003. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

B Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Complete if Known Substitute for form 1449A/B/PTO 10/615,716 Application Number **INFORMATION DISCLOSURE** Filing Date July 8, 2003 STATEMENT BY APPLICANT First Named Inventor Mladen MERCEP Art Unit TBA (Use as many sheets as necessary) Examiner Name TBA 03818/100L650-US1 3 of . 4 Attorney Docket Number Sheet

|                  | 144 | 14' + 11 A - A - 1 40 A AA + A + b - 1'- a - a - a - a - b da a R D - a b da a - C - d AA - a - b' da a   |  |
|------------------|-----|---|--|
| Ĉz,              | 41. | Kirst, H.A. et al., "34. Metabolism of macrolides," Bryskier, A. J. et al., Ed. Macrolides, Chemistry, Pharmacology and Clinical Use; Bryskier, Arnette Blackwell: Paris, 1993; pp 485- 491   |  |
| · )0             | 42. | Ma, Z. et al., "Discovery and Development of Ketolides as a New Generation of Macrolide Antimicrobial Agents," Current Medicinal Chemistry - Anti-Infective Agents, 1, 2002, 15-34  |  |
| 4,               | 43. | Pascual A. et al., "Uptake and intracellular activity of ketolide HMR 3647 in human phagocytic and non-phagocytic cells," Clin. Microbiol. Infect., 7, 2001, 65-69  |  |
| <del></del>      | 44. | Hand, W. L. et al., "Characteristics and mechanisms of azithromycin accumulation and efflux in human polymorphonuclear leukocytes," Int. J. Antimicrob. Agents, 18, 2001, 419-425   |  |
| 1.3              | 45. | Amsden, G. W., "Advanced-generation macrolides: tissue-directed antibiotics," Int. J. Antimicrob. Agents, 18, 2001, 11-15   |  |
| i,               | 46. | Johnson, J. D. et al., "Antibiotic uptake by alveolar macrophages," J. Lab. Clin. Med., 95, 1980, 429-439   |  |
| i <sub>y</sub> , | 47. | Wildfeuer, A. et al., "Uptake of Azithromycin by Various Cells and Its Intracellular Activity under In Vivo Conditions," Antimicrob. Agents Chemother., 40, 1996, 75-79   |  |
| 5.               | 48. | Scorneaux, B. et al., "Intracellular Accumulation, Subcellular Distribution, and Efflux of Tilmicosin in Chicken Phagocytes," <i>Poult. Sci.</i> , 77, 1998, 1510-1521  |  |
| Ċj.              | 49. | Mtairag, E. M. et al., "Investigation of dirithromycin and erythromycylamine uptake by human neutrophils in vitro," J. Antimicrob. Chemother. 33, 1994, 523-536   |  |
| Zy.              | 50. | Anderson R. et al., "An in-vitro evaluation of the cellular uptake and intraphagocytic bioactivity of clarithromycin (A-56268, TE-031), a new macrolide antimicrobial agent," <i>J. Antimicrob. Chemother.</i> , 22, 1988, 923-933    |  |
| <i>Ly</i> *      | 51. | Tasaka, Y. et al., "Rokitamycin Uptake by Alveolar Macrophages," Jpn. J. Antibiot. 41, 1988, 836-840  |  |
| 4,               | 52. | Harf, R. et al., "Spiramycin uptake by alveolar macrophages," J. Antimicrob. Chemother., 22, 1988, 135-140  |  |
| 40               | 53. | Suzuki, T. et al., "General and facile method for determination of configuration of steroid-17-yl-methyl glycolates at C-20 based on kinetic examination," <i>Chem. Soc.</i> , Perkin Trans. 1, 1998, 3831-3836                       |  |
| l,               | 54. | McLean, H.M. et al., "Novel Fluorinated Antiinflammatory Steroid with Reduced Side Effects: Methyl 9α-Fluoroprednisolone-16-carboxylate," <i>J. Pharm. Sci.</i> 1994, 83, 476-480   |  |
| i,               | 55. | Little, R.J. et al., "Soft Drugs Based on Hydrocortisone: The Inactive Metabolite Approach and Its Application to Steroidal Antiinflammatory Agents," Pharm. Res., 16, 1999, 961-967  |  |
| ·y               | 56. | Kertesz, D.J. et al., "Thiol Esters from Steroid 17β-Carboxylic Acids: Carboxylate Activation and Internal Participation by 17α-Acylates," J. Org. Chem., 51, 1986, 2315-2328   |  |
| i,               | 57. | Phillipps, G. et al., "Synthesis and Structure - Activity Relationships in a Series of Antiinflammatory Corticosteroid Analogues, Halomethyl Androstane-17β-carbothioates and 17β-carboselenoates," J. Med. Chem. 37, 1994, 3717-3729 |  |
| Ły.              | 58. | Bright, G.M. et al., "Synthesis, In Vitro and In Vivo Activity of Novel 9-Deoxo-9a-AZA-9a-<br>Homoerythromycin A Derivatives; A new Class of Macrolide Antibiotics, the Azalides" J. Antibiot., 41, 1998, 1029-1047                   |  |
| i.;              | 59. | Costa, A.M. et al., "Hybrids of macrolides and nucleobases or nucleosides," Tetrahedron Letters, 41, 2000, 3371-3375  |  |

| Examiner  | 1 1.10   | Date       | 2 154  |
|-----------|----------|------------|--------|
| Signature | El. Text | Considered | 3/3/2/ |



PTO/S8/08a/b (06-03)

Approved for use through 07/31/2003. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE on Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

| Sub   | Substitute for form 1449A/B/PTO                          |      | Complete if Known |                        |                   |
|-------|--|------|-------------------|------------------------|-------------------|
|       |  |      |                   | Application Number     | 10/615,716        |
| 11    | <b>IFORMATIO</b>   | N DI | SCLOSURE          | Filing Date            | July 8, 2003      |
| S     | STATEMENT BY APPLICANT (Use as many sheets as necessary) |      |                   | First Named Inventor   | Mladen MERCEP     |
|       |  |      |                   | Art Unit               | ТВА               |
|       |  |      |                   | Examiner Name          | TBA               |
| Sheet | 4  | of   | 4                 | Attorney Docket Number | 03818/100L650-US1 |

| Ép | 60. | Newman, S.P. et al., "Evaluation of jet nebulisers for use with gentamicin solution," <i>Thorax</i> , 40, 1985, 671-676   |  |
|----|-----|---|--|
| 59 | 61. | Berenberg, M.J. et al., "Comparison of Metered-Dose Inhaler Attached to an Aerochamber with an Updraft Nebulizer for the Administration of Metaproterenol in Hospitalized Patients," J. Asthma USA, 22, 1985, 87-92 |  |

<sup>\*</sup>EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

M:\3818\1L650US1\00044185.DOC

| Examiner  | 1, 12 22 | Date              |
|-----------|----------|-------------------|
| Signature | 1. Pala  | Considered 3/1/07 |

<sup>&#</sup>x27;Applicant's unique citation designation number (optional). <sup>2</sup>Applicant is to place a check mark here if English language Translation is attached.